Docket No.: SYN-00084 PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of	:	
Jacobus M. LEMMENS et al.	:	Examiner: S. Gollamudi
Serial No.: 09/938,816	:	Group Art Unit: 1616
Filed: August 27, 2001	:	

For: PHARMACEUTICAL COMPOSITIONS COMPRISING AMLODIPINE MALEATE

TRANSMITTAL OF APPEAL BRIEF

Commissioner of Patents and Trademarks
P.O. Box 1450
Alexandria, VA 22313-1450

September 14, 2004

Sir:

Further to the Notice of Appeal filed June 14, 2004, applicants submit herewith an Appeal Brief under 37 C.F.R. § 41.37. Also submitted herewith are:

(a) The fee pursuant to § 41.20 for filing an Appeal Brief in the amount of $330.00; and

(b) A petition for a one (1) month extension of time including the fee of $110.00.

Please charge any shortage in fees, or any overpayment, in connection with this filing, including extension of time fees, to Deposit Account No. 50-2877.

Respectfully submitted,

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PATENT

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Table of Contents

Page

I. Real Party in Interest 1

II. Related Appeals and Interferences 1

III. Status of Claims 2

IV. Status of Amendments 2

V. Summary of Claimed Subject Matter.....2

VI. Ground of Rejection to be Reviewed on Appeal.....3

VII. Arguments 4

VIII. Claims Appendix .....

IX. Evidence Appendix .....

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September 14, 2004

Sir:

This is an appeal from the rejection of claims 1, 2, 4-22, 28-33, and 37-47 of the above-identified application as set forth in the Office Action dated March 12, 2004. For the reasons set forth hereinafter, reversal of each of the Examiner's rejections is respectfully requested.

I. Real Party in Interest

The real party in interest is Synthon BV, a corporation of The Netherlands, having an office at Microweg 22, Nijmegen, The Netherlands.

II. Related Appeals and Interferences

There are no appeals or interferences, previously or currently, that are related to this application.

III. Status of Claims

Claims 1, 2, 4-22, 28-33, and 37-47 (all pending claims) are rejected.

Claims 3 and 23-27 have been cancelled.

Claims 34-36 are unentered.

IV. Status of Amendments

Subsequent to the filing of the RCE, no final rejection has been issued and thus ***no*** amendments after final rejection have been filed. Accordingly, the claims remain as rejected in the last office of March 12, 2004.

V. Summary of Claimed Subject Matter

The present application contains two independent claims; claim 1 directed to a pharmaceutical composition and claim 16 directed to a process.

Claim 1

Independent claim 1 relates to a pharmaceutical composition comprising an effective amount of amlodipine maleate and at least one pharmaceutically acceptable excipient. The composition is in solid form, such as a tablet or capsule, and has a pH within the range of 5.5-6.8. Support for the amlodipine maleate pharmaceutical composition including at least one excipient and the effective amounts thereof can be found, *inter alia*, on page 2 lines 20-21; page 4 line 16 through page 5 line 15; and page 5 lines 16-33 of the instant specification. Support for the pH range of 5.5 to 6.8 can be found on page 3 lines 2 and 22 of the instant specification. The pH for the claimed solid composition is determined by measuring a 20 wt% aqueous slurry, as is conventional for determining the pH of a solid material in this art, and is described, *inter alia*, in the

paragraph bridging pages 3 and 4 of the present specification. Support for the composition being in solid form can be found on page 7 lines 8-10 of the specification.

Appellants discovered that a pH within the range of 5.5 to 6.8 improves the stability of an amlodipine maleate solid pharmaceutical composition. Within the specified pH range, the degradation of the amlodipine maleate, especially the conversion of amlodipine maleate to "amlodipine aspartate," a previously undisclosed degradation product that proved to be quite problematic, is reduced.[1] As explained on page 3 of the instant specification, amlodipine aspartate is formed by a Michael addition reaction between the terminal amine group of amlodipine and maleic acid. The reaction is favored by higher pH values. Alternatively, low pH values encourage the formation of other amlodipine degradation reactions. Thus, the claimed pH range corresponds to the discovery of a stability sweet spot for solid amlodipine maleate pharmaceutical compositions.

Claim 16

Independent claim 16 relates to a process that comprises mixing amlodipine maleate and at least one pharmaceutically acceptable excipient to form a mixture having a pH within the range of 5.5 to 6.8. Support for the process can be found in original claim 16, page 3 line 22 (for pH 6.8 limit), and page 7 lines 20-24. The process is useful, *inter alia*, in making tablets or capsules within the scope of claim 1.

VI. Grounds of Rejection to be Reviewed on Appeal

1. Whether claims 1, 2, 4-7, 9, 11, 14-18, 22, 37-41, and 43-47 are unpatentable under 35 U.S.C. § 103 over Davison et al., US 4,879,303.

[1] The novel compound, amlodipine aspartate, was separately patented in commonly owned US 6,479,525. The present application and the application that matured into the 6,479,525 patent have the same filing and priority dates.

2. Whether claims 12 and 13 are unpatentable under 35 U.S.C. § 103 over Davison et al., US 4,879,303, in view of EP 0089167.

3. Whether claims 10, 19, and 20 are unpatentable under 35 U.S.C. § 103 over Davison et al., US 4,879,303, in view of Sherwood et al, US 5,585,115.

4. Whether claims 21, 32, and 33 are unpatentable under 35 U.S.C. § 103 over Davison et al., US 4,879,303, in view of Sherwood et al, US 5,585,115 and further in view of Schobel, US 4,687,662.

5. Whether claims 8, 28-31, and 42 are unpatentable under 35 U.S.C. § 103 over Davison et al., US 4,879,303, in view of Takatsuka et al., US 6,471,946.

6. Whether claims 8, 19, 20, 28-31, and 42 are unpatentable under 35 U.S.C. § 103 over Davison et al., US 4,879,303, in view of Toth et al, WO 98/26765.

VII. Arguments

1. Rejection over Davison et al

Claims 1, 2, 4-7, 9, 11, 14-18, 22, 37-41, and 43-47 stand rejected as being unpatentable under 35 U.S.C. § 103 over Davison et al., US 4,879,303 (hereinafter "Davison"). Appellants respectfully submit that this rejection is in error and request reversal thereof.

a. No *Prima Facie* Case of Obviousness - No Suggestion of pH Range

Davison fails to render obvious the claimed invention because Davison does not teach or suggest a solid amlodipine maleate pharmaceutical composition having the claimed pH. In fact, Davison is silent as to the pH of any solid amlodipine salt-containing pharmaceutical composition; and provides no disclosure of pH as being a parameter in designing solid pharmaceutical compositions of improved stability or any

other property. Nothing in Davison teaches or suggests the appellants' claimed pH range of 5.5 to 6.8, much less in combination with amlodipine maleate in a solid pharmaceutical composition.

Instead, Davison teaches that the besylate salt of amlodipine is the best suited for making pharmaceuticals and mentions amlodipine maleate as one of several comparative and inferior salts of amlodipine. The point of the Davison disclosure is to compare various salts of amlodipine to prove which one is the best; e.g. a selection invention from amlodipine salts. (See Davison col. 1 lines 29-35; col. 2 lines 6-13; col. 4 lines 21-26; and claim 1). Indeed, Davison specifically teaches that solid pharmaceutical compositions containing amlodipine maleate are much less stable than the compositions containing the besylate salt of amlodipine. (Davison col. 3 Table, lines 1-10). Far from teaching how to modify an amlodipine maleate-containing pharmaceutical composition, Davison teaches avoiding amlodipine maleate in favor of the besylate salt of amlodipine. (See Davison col. 2 lines 15-18; and col. 4 lines 22-26). Nothing in Davison teaches controlling the pH of any amlodipine salt pharmaceutical composition in order to improve stability, or for any other reason. In short, Davison is silent regarding the pH of a solid pharmaceutical composition and only mentions amlodipine maleate as one of the known, inferior salts to the besylate salt.

In view of these shortcomings, Davison is incapable of creating a *prima facie* case of obviousness. There is no teaching or suggestion in Davison motivating the worker of ordinary skill in the art to select (1) amlodipine maleate and (2) formulate it to have a pH within the range of 5.5 to 6.8. Davison teaches away from using amlodipine maleate: Davison is silent as to the pH of a solid pharmaceutical composition. In the absence of

some motivation to select the claimed pH range for amlodipine maleate-containing solid pharmaceutical compositions, the rejection can not establish a *prima facie* case of obviousness. *In re Dance*, 160 F.3d 1339, 1343 (Fed. Cir. 1998). Indeed, strict application of the requirement for motivation in a rejection under § 103 is necessary to prevent the "subtle but powerful attraction of an [improper] hindsight-based obviousness analysis." *In re Dembiczak*, 175 F.3d 994, 999 (Fed. Cir. 1999). Without the requisite guidance in the applied prior art to select the appellants' claimed pH range, the formation of the presently claimed subject matter could not have been obvious over Davison within the meaning of § 103. For this reason alone, reversal of the rejection is appropriate and requested.

b. The Errors in the Examiner's Rejection

While the above analysis should end the matter, the rejection is complicated by the Examiner's numerous errant readings of Davison and unsubstantiated assertions. Accordingly, to help clarify the issues, three of the most prominent of the Examiner's errors are explained below.

Davison Does Not Teach Composition pH - Only Salt pH

The first error is derived from Davison column 2, lines 22-31, especially 26-31, which the Examiner reads as teaching "the preferred pH of the ***composition*** to be close to that of blood pH 7.4 because it can be readily biocompatible." (See, *inter alia*, Office Action 11/04/2002, page 2, fourth and fifth line from the bottom (emphasis added)). From this passage in Davison column 2, the Examiner purports to have motivation to make a solid pharmaceutical composition having a pH near 7.4 and that "near" 7.4 is close enough to embrace 6.8 of the present claims.

But in fact this passage in column 2 relates to the water solubility and bioavailability of amlodipine salts - not the solid composition. The texts reads: "[i]n addition, ***salts*** which provide solutions having a pH close to that of blood (7.4) are preferred because they are readily biocompatible and can easily be buffered to the required pH range without altering their solubility." (Davison col. 2 lines 26-31 (emphasis added)). The passage is directing the selection of an amlodipine salt; not how to formulate a solid amlodipine composition. Davison itself teaches that the water solubility/pH properties are the first of four properties used to evaluate which amlodipine salt to use. (See Davison col. 2 lines 8-13). The pH in Davison is a criterion for picking a salt of amlodipine so that solutions thereof, not solid compositions, are biocompatible with blood.

Further, such a teaching is irrelevant to the pH of a ***solid*** pharmaceutical composition such as a tablet, that is not intended to contact the blood stream; e.g., tablets are not commonly injected into the blood stream. A tablet is normally ingested, the active agent is released and generally dissolved in the gastro-intestinal fluid, and then absorbed into the blood stream. It is the active agent and/or its salt that is absorbed, not the solid pharmaceutical composition. The pH of the salt, as taught in Davison, could be a factor in bioavailability/biocompatibility and hence it is used as a selection criterion for choosing a salt of amlodipine. But the pH of the solid pharmaceutical composition relative to its biocompatibility in blood is nonsensical.

Thus, the desire in Davison to have a "pH close to that of blood (7.4)" refers only to the amlodipine salt to be selected, not the solid pharmaceutical composition containing it. There is no teaching, suggestion or guidance in Davison column 2 lines 22-36 (or

elsewhere) of controlling the pH of a solid pharmaceutical composition to be close to that of blood, or any other pH. Because the pH mentioned in Davison refers to the salt of amlodipine and not to the pH of any solid pharmaceutical composition, the worker of ordinary skill in the art is not motivated by Davison to adjust, or even experiment with, the pH of an amlodipine-containing solid pharmaceutical composition, as alleged by the Examiner. The Examiner's purported motivation is nonexistent. In the absence of any motivation to adjust the pH of a solid pharmaceutical composition, the formation of the appellants' claimed solid amlodipine maleate-containing pharmaceutical composition having a pH of 5.5 to 6.8 could not have been obvious over Davison.

Davison Does Not Teach That pH Improves Stability

Another error stems from the Examiner's insistence that Davison teaches pH to be a result-effective parameter in designing solid pharmaceutical compositions. Specifically, the Examiner stated:

> "One of ordinary skill in the art would be motivated to select the proper pH based on Davison' [sic] teachings on column 2, line 47 wherein he states that good stability in solid state is very important for tablets and capsules. Thus, one can come to the conclusion that a solid state should have a proper pH, which contributes to stability."

(Office Action 05/05/2003 page 3 line 19 to page 4 line 1). But line 47 of Davison, which begins the second enumerated criteria for evaluating amlodipine salts, makes no mention of pH. The remaining discussion of stability in Davison (column 2 line 47 to column 3 line10) does not mention pH (or solubility for that matter). While good stability is desired by Davison, the point of column 2 line 47 to column 3 line 10 is to

determine which salt of amlodipine has the best chemical stability; i.e., achieve good stability by picking the best salt of amlodipine. Nothing here indicates that the stability of an amlodipine maleate solid pharmaceutical composition can be improved by selecting a pH range, much less that the appellants' claimed range of 5.5 to 6.8 provides for improved stability.

In effect, the Examiner has combined the separate criteria of solubility and stability taught in Davison column 2 to conclude that the pharmaceutical composition's stability can be improved by controlling the pH to be about that of blood. In reality the water solubility criteria, and its reference to pH, is a separate criteria from the stability criteria. Reading them together to say that stability is improved by setting the pH to close to 7.4, as the Examiner has done, is a clearly erroneous interpretation of the Davison teachings. There is no teaching in Davison of using pH to improve the stability of a solid pharmaceutical composition or that pH is a result-effective parameter.

The Examiner's construction is also illogical. If Davison taught that controlling pH improved the stability for all amlodipine salt-containing solid pharmaceutical compositions, then good stability would not be a selection criterion for choosing the amlodipine salt. That is, under the Examiner's reading, the choice of amlodipine salt would be independent of stability and a solid pharmaceutical composition of any amlodipine salt would be expected to have good stability as long as a pH of about 7.4 was established. But the data in Davison column 3 lines 1-10 shows that the different salts of amlodipine do have different chemical stabilities, and importantly does not attempt to identify, much less correlate, the composition's pH with its stability.[2] The Examiner's

[2] Interestingly, the data also shows that stability does not increase as the pH of the amlodipine salt approaches 7.4. Note that the mesylate salt has the second highest stability but has a very low salt pH of

understanding of Davison destroys the very point of the patent; namely that the besylate salt of amlodipine was found to be the best salt based on the four enumerated selecting criteria. Neither logic nor the text of Davison comport with the Examiner's positions. Therefore, the examiner's assertion that Davison suggests using a "proper pH" to improve the stability of a solid amlodipine maleate pharmaceutical composition is not supported by, and is fundamentally inconsistent with, the teachings in Davison.

Because there is no teaching in Davison to use pH to improve the stability of the solid pharmaceutical composition, the Examiner's conclusion that the claimed pH range is a mere unpatentable optimization is without merit. Only the optimization of a known result-effective variable could be considered obvious. *In re Aller*, 220 F.2d 454 (CCPA 1955). But, it can not be obvious to optimize a variable that was not recognized to be a result-effective parameter. *In re Antonie*, 559 F.2d 618, 620 (CCPA 1977). Davison does not disclose the amlodipine aspartate degradation product or its mechanism of formation. In the absence of any knowledge of the degradation compound and its formation, it would have been impossible for the worker of ordinary skill in the art to have found it obvious to prevent the unknown compound's formation by controlling the pH of the composition. Simply trying every variable until the composition works better is not an obvious optimization; e.g., "obvious to try" is not the standard of § 103. *Id.* To be obvious under § 103, the prior art must provide some guidance or motivation. *Dance, Supra.* Davison does not provide that guidance or motivation; i.e., no relationship between the stability of amlodipine maleate-containing solid pharmaceutical

3.1. Thus, in no way does Davison hint that pH correlates with stability or that a pH of a salt or a composition close to blood improves stability.

compositions and the pH of the composition. Accordingly, the Examiner's conclusion of obviousness is legally and factually in error.

No Implicit Composition pH Teaching in Davison

The Examiner also asserts that Davison implicitly teaches the worker of ordinary skill in the art to adjust the pH of the pharmaceutical compositions because "Davison teaches sodium glycollate and dibasic calcium phosphate, which are routinely utilized in the art to adjust pH to, [sic] desired level." (Office Action 03/12/2004 page 4 lines 8-10). Not so. Dibasic calcium phosphate and sodium starch glycollate are not "routinely" used as pH adjusting agents in solid pharmaceutical compositions, nor would their presence imply to the reader that pH is being controlled or adjusted. The basis for the Examiner's statement is unknown. Nothing in the present record supports the Examiner's position. The Examiner can not base rejections on "subjective belief and unknown authority." *In re Sang*, 277 F.3d 1338, 1334 (Fed. Cir. 2002). In the absence of any evidence to support the Examiner's position, the Examiner's naked assertion should be rejected.

Furthermore, Appellants believe the Examiner's position is patently false for the following reasons. Dibasic calcium phosphate is typically utilized as a diluent in tablets and capsules. The Handbook of Pharmaceutical Excipients (See Exhibit A in Evidence Appendix IX) describes the "functional category" of dibasic calcium phosphate as a "tablet and capsule diluent" for both anhydrous and dihydrate forms. The uses for these materials, as described in the "Application in Pharmaceutical Formulation or Technology" section, do not include utility as pH adjusting agents. If this use was so well known and routine, one would have expected the Handbook of Pharmaceutical Excipients to at least mention it. But it does not. Further, given that the Handbook

recognizes that the pH of commercially available dibasic calcium phosphate anhydrous varies by supplier and grade, i.e. typical pH=7.3 but A-Tab pH=5.1, it appears that the recitation of an "anhydrous dibasic calcium phosphate," would not inform the reader as to which way the pH was being adjusted, if at all. Thus, the Examiner maintains that dibasic calcium phosphate is so "routinely" used as a pH adjusting agent and that workers skilled in the art would recognize the mentioning of such as an adjustment of the pH of the composition, even though the adjusting effect on the pH (i.e. up or down), if any, would be unknowable. Such an illogical premise cannot and should not be accepted as true without some evidence from the prior art attesting thereto.

Regrettably, it appears that the Examiner has confused dibasic calcium phosphate, a solid material commonly found inside pharmaceutical tablets, with an aqueous phosphate buffer solution. The Examiner has even cited Methods in Enzymology, referring to phosphate buffer stock solutions, for the proposition that calcium phosphate buffers can only have a pH between 5.7 and 8.0. (See Office Action 05/05/2003 page 4 lines 10-12). Appellants agree that aqueous buffer solutions are indeed related to pH, e.g. to stabilizing/maintaining a pH, but no such pH relationship exists for dibasic calcium phosphate (a solid) in solid pharmaceutical compositions. The use of dibasic calcium phosphate does not alert the worker of ordinary skill in the art to adjust the pH of the tablet composition, but rather serves to inform the reader of a useful diluent for tabletting.

Similarly, sodium starch glycollate is routinely used as a disintegrant in pharmaceutical tablets; i.e. as an agent that helps tablets to break apart in the stomach and release the active agent. Davison describes sodium starch glycollate as a disintegrant, not as a pH adjusting agent (See Davison col. 1 lines 48-49). There is no basis on this record,

and appellants are aware of none, to conclude that sodium starch glycollate is "routinely used" as a pH adjust agent.

In summary, while calcium phosphates and sodium starch glycollate can have an effect on pH, such a utility is not the primary or routine use of these excipients as the Examiner alleges; i.e. dibasic calcium phosphate is not a buffer solution. The mere mention of such pharmaceutical excipients does not inform the worker of ordinary skill in the art to adjust the pH of the composition. Accordingly, Davison does not implicitly or otherwise suggest adjusting the pH of a solid pharmaceutical composition and certainly does not suggest forming an amlodipine maleate-containing solid pharmaceutical composition having a pH within the range of 5.5 to 6.8. Therefore, the Examiner has no motivation for modifying the prior art to obtain the claimed invention and the rejection under § 103 should be reversed.

In view of the true disclosure in Davison, including the lack of any suggestion to modify the pH of a solid pharmaceutical composition, much less to formulate the pH of an amlodipine maleate-containing solid pharmaceutical composition to within the range of 5.5 to 6.8, the lack of any suggestion that the compositions pH would solve stability problems for amlodipine maleate, and the lack of any suggestion of how to improve the stability of the amlodipine maleate, the Examiner's rejection fails to provide any motivation to make the claimed invention. Therefore, the Examiner has failed to establish a prima facie case of obviousness and reversal of this rejection one this basis alone is warranted.

c. Secondary Considerations

Notwithstanding the foregoing arguments, the patentability of the claimed subject is even more clear when viewed in light of the evidence of non-obviousness; i.e., the secondary considerations. In particular, the prior failure of others to successfully stabilize amlodipine maleate and the unexpectedly superior stability over the claimed pH range serves to rebut any *prima facie* case of obviousness.

Failure of Others - Surprising Success

Amlodipine was disclosed in US 4,572,909; the maleate salt being preferred. This original preference is acknowledged in Davison, which is commonly owned with US 4,572,909 by Pfizer Inc. (See Davison col. 1 lines 25-26). In fact, originally Pfizer planned to market amlodipine maleate and even developed the product sufficiently to conduct clinical trials. But there was a problem with amlodipine maleate. The publicly available portions of a "Review of an Original NDA" for the product amlodipine besylate (sold as NORVASC® by Pfizer) reveal that:

> Pfizer originally intended to market the maleate salt of amlodipine. As a result, clinical studies were conducted with amlodipine maleate tablets and capsules (the capsules were used by the European counterparts). The ***maleate salt however, had formulation (tabletting) and stability problems***. The firm therefore switched to the besylate salt of amlodipine.

(Exhibit B, Evidence Appendix IX, FDA FOIA Material on Amlodipine Besylate, page 2, lines 4-8 (emphasis added)). Thus, Pfizer failed to solve the tabletting and stability problems that occurred with amlodipine maleate solid pharmaceutical compositions. Instead of solving the problems with the maleate salt, Pfizer sought to switch salts. This

effort lead to the besylate salt of amlodipine and the filing and granting of the Davison patent.

In contrast, the present invention improves the stability of amlodipine maleate. In fact, the amlodipine maleate compositions of the presently claimed invention can have good stability that is equal to or superior over the besylate salt of amlodipine, e.g., Pfizer's NORVASC commercial product. The following table presents some of the data from pages 17 and 18 of the present specification.

Month	Example 1 Sample (A) mg of Amlodipine	NORVASC® 2.5mg US mg of Amlodipine
0	2.45	2.44
3	2.40	2.34

This data shows that under accelerated storage conditions commonly used for measuring stability (storage in an open dish at 40°C/75%RH), inventive sample A lost 0.05 mg of amlodipine (2.45-2.40 = 0.05) during three months while the commercial amlodipine formulation using the besylate salt lost twice as much amlodipine, namely 0.1 mg of amlodipine (2.44-2.34 = 0.1). This loss of amlodipine between time 0 and 3 months is due to various degradation reactions that are consuming the amlodipine. Accordingly, the smaller the change in amlodipine content, the better the stability. In this case, inventive sample A, which contains amlodipine maleate and has a pH of 6.13 (see page 10 of the instant specification), has a lower change in amlodipine content and is equal to or more stable than the commercial besylate salt of amlodipine formulation.

The presently claimed invention can achieve that which the prior art could not: commercially stable amlodipine maleate compositions. Whereas Pfizer found it easier to switch salts (and undoubtedly spend extra time and money in conducting additional tests for approval), the present invention has instead solved those problems. The fact that the salt switch was made after clinical trials were already begun only furthers the worker of ordinary skill in the art's belief that the amlodipine maleate stability problems were non-trivial and apparently not easily solved; else Pfizer would have stayed with the clinically tested maleate salt and simply adjusted the formulation. Overcoming the failure of others, and in this case the originator's failure, is strong evidence from the real world of non-obviousness.[3] Such evidence must be considered in any obviousness determination, *In re Piasecki*, 745 F.2d 1468 (Fed. Cir. 1984).

Unexpected Results in Comparison to the Foundation for Obviousness

Moreover, in an effort to expedite prosecution appellants made of record a showing to test the Examiner's theory of obviousness. (See Exhibit C, Evidence Appendix IX, Rule 132 Declaration of Ing. Vanderheijden). The Declaration compares four tablets of the invention (pH = 5.8, 5.95, 6.07, and 6.36) against a tablet composition above the claimed pH (pH = 7.2) and below the claimed pH (pH = 5.19). The tablets were subjected to accelerated stability studies and the results from the 'warm and humid' testing conditions are reproduced below.

[3] It is ironic that the Examiner holds the appellants' solution to the amlodipine maleate composition problem to have been obvious from the Pfizer patent resulting from the research for switching from the maleate to the besylate salt.

Table 2A

Difference in Impurities Between 40°C/75% RH and Baseline After 1 month, Open Dish

	A pH 7.2	B pH 6.36	C pH 6.07	D pH 5.95	E pH 5.8	F pH 5.19
Δ Aspartate[1]	5.11	1.55	0.30	0.07	0.06	0.05
Δ Amide[2]	0	0	0	0	0.04	0.13
Δ Pyridine[3]	0.09	0.05	0.03	0.05	0.10	0.13
Δ Total Impurities	5.68	1.73	0.4	0.19	0.25	0.42

1. amlodipine aspartate (Z#204)
2. amlodipine amide (Z#205)
3. amlo-pyridine (Z#202)

According to the Examiner's theory, the pH of 7.2, being near to that of blood, should be the best, most stable. But it was not. In fact it was the least stable, producing a large amount of amlodipine aspartate (an increase of 5.11). Thus, following the 'Davison teaching' as understood by the Examiner, to use a pH of around 7.4 actually contributes to the enhanced formation of the aspartate degradation product. "Surprisingly," solid compositions with an acidic pH that is farther removed from that of blood, and within the claimed range of 5.5 - 6.8, provide for enhanced stability performance. The superior performance of the claimed compositions having a pH of 5.5 to 6.8 is therefore unexpected and unobvious over the teachings of Davison, even as misconstrued by the Examiner.

In addition to showing unexpected results, the data shows and confirms the overall trend reported in the instant specification, namely that the stability 'sweet spot' for a solid amlodipine maleate pharmaceutical composition is a pH between 5.5 and 6.8. At a pH of 7.2 the amount of aspartate formed significantly increases (see tablet A). As explained on page 3 of the specification, it is believed that the aspartate is formed in the

solid composition via a Michael addition, which needs an alkaline environment. On the other hand, as the pH drops below 5.5, the formation of other impurities, such as amlopyridine, increases. Thus, appellants are claiming the optimized pH range for reducing the risk of instability. Without knowledge of these impurities or their mechanisms of formation, however, it would not be possible to predict that pH could be used to improve stability or that an optimum pH existed. Since Davison does not recognize the aspartate impurity, nor its mechanism of formation, Davison likewise offers no suggestion to control pH to the appellants' claimed range or any reasonable expectation of improving stability thereby.

The data compares a tablet composition that is closer to the presently claimed invention than the hypothetical Davison composition suggested by the Examiner. That is, appellants have compared not merely to a pH of 7.4 but rather have made an even closer comparison using a pH of 7.2 in tablet A. Such a comparison satisfies the requirement to compare against the closest prior art. *Ex parte Humber*, 217 USPQ 265 (POBA 1981). Further, the data is commensurate in scope with the claims. Note that a pH of 6.8 is about half-way between the compared values of 7.2 and 6.36 (tablets A and B, respectively) and less than half-way between the Examiner's proposed 7.4 and the tested 6.36. The trend in the data also supports 6.8 as being a reasonable cut-off. Finally, given the theory of how the aspartate is formed by way of a reaction requiring alkaline conditions, the 6.8 upper limit is a reasonable scope of protection, i.e., sufficiently less than alkaline to help reduce/avoid aspartate instability issues. Therefore, the data in the Declaration properly compares against the cited prior art and shows/confirms the unexpectedly superior and unobvious results that are achieved by the present invention.

The Examiner minimizes the value of the Declaration evidence through various criticisms. These criticisms are factually and/or legally unsound. For example, the Examiner dismisses the unexpectedly superior showing regarding stability of the claimed amlodipine maleate compositions because the claims do not recite improved stability (Office Action 05/05/2003 page 5 lines 15-17). But the law does not require applicants to recite advantages that flow from the claimed invention. Instead, the claims need only recite the structure/function that provides those advantages. *In re Merchant*, 575 F.2d 865, 869 (CCPA 1978)("We are aware of no law requiring that unexpected results relied upon for patentability be recited in the claims. . . Moreover, the 'feature' responsible for appellant's unexpected results is recited in the claims, viz., 'substantially anhydrous.'"); *Ex parte Rinderer*, appeal No. 2000-1651, 2002 WL 465339 (BPAI 2002)("In order to distinguish the claims over the prior art, an applicant is not required to recite the advantages flowing from the claimed invention; rather the claims must include the structure which provides those advantages"). In the instant application, the claims recite the feature from which the unexpected results flow, namely controlling the pH to the specified range.

Similarly, the Examiner misapplies the notion of a showing being not commensurate in scope with the claims. According to the Examiner, testing one tablet formulation with a variety of different pH values can only support a claim limited to that exact formulation. (Office Action 03/12/2004 page 5 lines 1-6). This is not the law. The non-obviousness of a genus can be established by testing a few species, so long as the "trend in the exemplified data which would allow the artisan to reasonably extend the probative value thereof." *In re Kollman*, 595 F.2d 48, 201 USPQ 193 (CCPA 1979).

Here, given the science behind the stability/degradation problem to be solved, the worker of ordinary skill in the art would expect the full range of excipients to provide similarly advantageous results; i.e., it is the pH that matters, not the specific ingredients. That the Examiner can propose variables which may affect the unexpected results is not a valid basis to disregard the showing. Instead, the Examiner must provide more than mere speculation. *Ex parte Nieh*, Appeal No. 1999-0381, 2002 WL 1801386 (BPAI 2002)("Assuming arguendo that these factors may have some effect, the examiner has provided no evidence to substantiate that they are of any significance. The examiner's position is speculative in nature absent an explanation or evidence of record of why these factors would be expected to affect the results to such a degree that the declaration evidence would be of minimal value"). The data in the Declaration provides a side-by-side comparison of formulations with only one change, the pH. Such a controlled experiment affords a better review of the effect of pH and should not be criticized as not being commensurate in scope with the claims.

But even if the Examiner had some concern that some other factor was responsible for the unexpectedly superior results shown in the Declaration, those concerns are answered by the data in the specification. That is, a variety of formulations, including capsules, are made and tested in the examples of the instant specification. These data show that with different solid formulations, formulations with a pH within the claimed range provide for unexpectedly superior results. The Examiner's position is thus factually and legally in error.

Finally, the Examiner criticizes the Declaration because it uses different accelerated storage conditions than Davison. (Office Action 03/12/2004 page 5 lines 6-

18). According to the Examiner, it is not possible to tell whether the appellants claimed invention is superior because the tests results in the Declaration can not be directly compared to the test results in Davison. But the Examiner's concern is misplaced. The trouble with the amlodipine maleate stability is conclusively established by both Davison and the FDA FOIA material. An direct comparison is not needed to establish the known prior art inferiority of amlodipine maleate compositions to the besylate salt of amlodipine. Secondly, the side-by-side comparison of the commercial NORVASC® material with the present invention in the instant specification shows that under the same storage conditions the inventive amlodipine maleate composition does not have inferior stability. (See pages 17-18 of the instant specification). Thus, a direct comparison has been made.

In view of the evidence, weighed in its totality, the selecting of the appellants' claimed pH range to solve the long standing stability problem with solid amlodipine maleate-containing pharmaceutical compositions could not have been obvious to the worker of ordinary skill in the art. Such evidence rebuts any prima facie case of obviousness the Examiner may have established. Accordingly, reversal of this rejection is requested.

d. Separate Patentability for Claims 37, 38, and 39

Claims 37 and 39 recite the pH as about 5.5 to 6.2, while claim 38 recites a pH range of about 6.0 to 6.2. These claims are separately patentable in that they are narrower in scope and thus less easily attacked as not being commensurate in scope with the data. That is, these claims are directed to the usually preferred embodiments of the invention. To the extent that the Board might decide that the data of record does not

compel the non-obviousness of the full scope of claim 1, these narrower claims are more surely clearly unobvious in view of the comparison test data found in the instant specification and the Declaration. Therefore, should the Board not reverse the present rejection, separate consideration and reversal of the rejection of these claims are requested.

2. Rejection over Davison in view of EP'167

Claims 12 and 13 stand rejected as being unpatentable under 35 U.S.C. § 103 over Davison in view of EP 0089167 (EP '167). Appellants respectfully submit that this rejection is in error and request reversal thereof.

The Examiner relies upon EP '167 only to show that the claimed dosage amounts of amlodipine maleate would have been obvious. But EP '167 does not overcome any of the deficiencies in Davison as set forth above, nor does the Examiner allege that EP '167 teaches or suggests a pH for an amlodipine maleate composition. Therefore, the combination of Davison with EP '167 fails to render the claimed subject matter obvious for the reasons set forth above. Reversal of this rejection is requested.

3. Rejection over Davison in view of Sherwood

Claims 10, 19, and 20 stand rejected as being unpatentable under 35 U.S.C. § 103 over Davison in view of Sherwood et al, US 5,585,115 (Sherwood). Appellants respectfully submit that this rejection is in error and request reversal thereof.

Sherwood is relied upon only as a general teaching of processes for making tablets and is not cited or asserted to teach the pH for an amlodipine composition of any kind. Therefore, for the reasons set forth above, the combination of Davison and

Sherwood is insufficient to render the presently claimed subject matter unpatentably obvious. Reversal of this rejection is requested.

4. Rejection over Davison in view of Sherwood and Schobel

Claims 21, 32, and 33 stand rejected as being unpatentable under 35 U.S.C. § 103 over Davison in view of Sherwood and further in view of Schobel, US 4,687,662 (Schobel). Appellants respectfully submit that this rejection is in error and request reversal thereof.

This rejection is in error for at least the reasons set forth above regarding the failures of Davison. Inasmuch as Davison is deficient to render claim 1 unpatentable and Sherwood and Schobel are not asserted to overcome these deficiencies, the instant rejection of dependent claim 21 is likewise improper. Moreover, the Examiner has misunderstood the teaching of Schobel. Specifically, Schobel teaches a granulate formed of excipients and a therapeutic agent as having a particle size of 100 to 600 microns. But claims 21, 32, and 33 refer to the particle size of the amlodipine maleate (active agent) per se, not to a granulate of the amlodipine maleate and some excipients. Schobel contains no teaching regarding the particle size of the therapeutic agent itself and thus does not teach or suggest the invention of claims 21, 32, or 33. Thus, for these additional reasons, reversal of this rejection is requested.

5. Rejection over Davison in view of Takatsuka

Claims 8, 28-31, and 42 stand rejected as being unpatentable under 35 U.S.C. § 103 over Davison in view of Takatsuka et al., US 6,471,946 (Takatsuka). Appellants respectfully submit that this rejection is in error and request reversal thereof.

Takatsuka is cited by the Examiner for teaching various organic acids as being useful pH adjusting agents. Appellants agree that Takatsuka discloses conventional pH adjusting agents. However, there is no motivation to combine the pH adjusting agents of Takatsuka with any of the teachings in Davison. That is, Davison does not, contrary to the Examiner's position, teach adjusting the pH of a solid pharmaceutical composition. Accordingly, there is no motivation to look to conventional pH adjusting agents as taught in Takatsuka in preparing the pharmaceutical compositions of Davison. Conversely, Takatsuka relates to an oral composition for treating teeth wherein the pH of the composition is preferably within the range of 6.5 to 8.5. This pH range avoids making the composition too astringent on the one hand and not too irritating to the oral mucosa on the other. (See Takatsuka col. 2 line 66 to col. 3 line 5). The pH range has nothing to do with delivering a dihydropyridine heart medication such as amlodipine, nor does it relate to stability of the composition. Instead, the pH simply recognizes that compositions contained in the oral cavity for significant times need to be accommodating to the pH environment so as to be comfortable to the user. Accordingly, Takatsuka has nothing to do with Davison or the present invention and the worker of ordinary skill in the art would have had no motivation to combine Takatsuka with Davison.

Moreover, even assuming that Davison did teach adjusting the pH of solid pharmaceutical compositions to around 7.4, as the Examiner insists, there is still no logical reason to combine acidic pH adjusters therewith. The pH of amlodipine maleate is stated in Davison to be 4.8. Thus, a base/alkaline agent would be the "obvious" choice for adding to the amlodipine maleate composition in order to help insure that the about

7.4 pH value was attained. An acidic pH adjusting agent would tend to bring the pH of the composition in the "wrong" direction, i.e., acidic and not alkaline.

The Examiner's hypothetical situation of a composition that has a pH higher than blood and thus would need an acidic pH adjusting agent does not provide proper motivation. Specifically, such a hypothetical overlooks the claimed pH range of 5.5 to 6.8. If the pH of a composition was greater than 7.4 and Davison taught using a pH around 7.4, what would motivate the average artisan to use too much acidic pH adjusting agent and drop the pH below 7.4, below 7.0, and down into the appellants' claimed range of 5.5 to 6.8? The answer is "nothing." It is simply illogical for a worker of ordinary skill in the art, if motivated to make a composition with a pH of about 7.4, to add acidic pH adjusting agents so as to obtain a pH within the acidic range of 5.5 to 6.8. Indeed, such a modification would be seen as counter productive and hence not obvious.

Aside from failing to create a *prima facie* of obviousness for want of proper motivation in the prior art, the unexpectedly superior results exhibited by the present invention over the claimed pH range establishes non-obviousness. That is, nothing in Davison or Takatsuka suggests that the pH range of 5.5 to 6.8 would provide for superior stability in an amlodipine maleate-containing solid pharmaceutical composition. Therefore, the formation of the presently claimed subject matter would not have been obvious to the worker of ordinary skill in the art. Reversal of this rejection is respectfully requested.

6. Rejection over Davison in view of Toth

Claims 8, 19, 20, 28-31, and 42 stand rejected as being unpatentable under 35 U.S.C. § 103 over Davison in view of Toth et al, WO 98/26765 (Toth). Appellants respectfully submit that this rejection is in error and request reversal thereof.

Toth is cited by the Examiner as allegedly suggesting the use of maleic acid in the composition of Davison to improve stability. This rejection has several errors.

Firstly, Toth is non-analogous prior art. Specifically, Toth relates to the ACE inhibitor enalapril and not to calcium channel blockers like amlodipine. The basic chemical structures of enalapril and amlodipine are unrelated. The well known hydrolysis and cyclization problems associated with enalapril and enalapril maleate are not taught to occur in amlodipine by Davison or any other art of record. Thus, Toth does not deal in the same field of endeavor as the present inventors, namely the calcium channel blocking dihydropyridine derivative known as amlodipine, nor is Toth directed to solving the same problem as appellants; e.g., the unknown stability problems of amlodipine maleate in a solid pharmaceutical composition. Accordingly, Toth is non-analogous prior art. *In re Clay*, 966 F.2d 656 (Fed. Cir. 1992). Therefore, the hypothetical worker of ordinary skill in the art is not charged with knowledge of Toth and the Examiner can not use Toth in making a rejection under § 103. *Id.*

Secondly, the rejection is improper because there is no reasonable expectation of success in applying the enalapril maleate specific teachings of Toth to other, non-analogous compounds. Toth teaches that enalapril maleate can be stabilized against hydrolysis and/or cyclization by incorporating additional maleic acid into the composition. In contrast, Davison does not indicate that amlodipine maleate suffers from

hydrolysis or cyclization. In the absence of some reason to believe that enalapril and amlodipine would suffer from similar degradation reactions, there is no reason to believe that the solution put forth in Toth for stabilizing enalapril maleate would be useful in improving the stability of amlodipine maleate. And, given the difference in chemical structure between amlodipine and enalapril, e.g. substituted dihydropyridine ring structure with a terminal amine group in amlodipine, there is no basis to believe that amlodipine would have a similar degradation pathway as enalapril. In fact, the degradation is very different, i.e., stopping the reaction of the terminal amine group of amlodipine with maleic acid to form amlodipine aspartate. Enalapril does not have a terminal amine moiety and thus does not present this possibility. Since Toth does not teach that maleic acid is a universal stabilizing agent, but rather is narrowly disclosed to be useful in stabilizing enalapril maleate, the worker of ordinary skill in the art would not reasonably expect the stability enhancing technique applied in Toth to enalapril to be useful in stabilizing amlodipine maleate.

Thirdly, there is no motivation to incorporate an acidic pH adjusting agent into Davison as proposed by the Examiner. Specifically, under the Examiner's reading, Davison desires a composition to have a pH of about 7.4. Given that this is an alkaline pH, it is unknown why the average artisan would reach for the use of an acidic pH adjusting agent. By the Examiner's logic, the worker of ordinary skill in the art would be avoiding acidic ingredients. Under a proper reading of Davison, there is no mention of the pharmaceutical composition's pH and hence again, no reason to incorporate an acidic pH adjusting agent. Absent improper hindsight reconstruction, nothing motivates the Examiner's proposed modification of Davison.

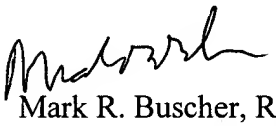
Fourthly, Toth and Davison each fail to teach or suggest the appellants' claimed pH range. While Toth teaches the use of maleic acid, there is no indication of the final pH of the composition. Davison teaches, according to the Examiner, a pH of about 7.4. Nothing in these two teachings suggests a pH of 5.5 to 6.8 for a solid pharmaceutical composition. Merely adding maleic acid to Davison does not necessarily result in the appellants' claimed pH range. Accordingly, neither disclosure leads the worker of ordinary skill in the art to the claimed invention.

Finally, the unexpected results demonstrated for the claimed pH range establishes non-obviousness. Neither Toth nor Davison teach that amlodipine maleate compositions are less stable above pH 6.8 and below pH 5.5. This range is not disclosed in either document and yet, appellants have shown that compositions having stability equal to compositions containing the besylate salt of amlodipine can be formed within this range. This surprising and superior effect manifests the non-obviousness of the claimed invention. Accordingly, considering the invention as a whole, it could not have been obvious to the worker of ordinary skill in the art to form the presently claimed invention from the combined teachings of Davison and Toth. Reversal of this rejection is respectfully requested.

7. Conclusion

For the reasons set forth above, each of the Examiner's rejections is in error and reversal thereof is respectfully requested.

Respectfully submitted,



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Listing of Claims:

1. A pharmaceutical composition comprising an effective amount of amlodipine maleate and at least one pharmaceutically acceptable excipient wherein said composition has a pH within the range of 5.5 - 6.8 and is in solid form.

2. The composition according to claim 1, wherein said composition has a pH of about 6.0 - 6.8.

3 (cancelled).

4. The composition according to claim 1, wherein said excipient is calcium phosphate or microcrystalline cellulose.

5. The composition according to claim 4, wherein said composition comprises calcium phosphate and microcrystalline cellulose.

6. The composition according to claim 4, wherein said excipient is calcium hydrogen phosphate.

7. The composition according to claim 4, wherein said excipient is microcrystalline cellulose.

8. The composition according to claim 1, wherein said composition further comprises an acidic pH adjusting agent.

9. The composition according to claim 1, wherein said composition is in the form of a tablet.

10. The composition according to claim 9, which further comprises an outer layer surrounding said tablet.

11. The composition according to claim 1, wherein said composition is in the form of a capsule.

12. The composition according to claim 1, wherein said amount of amlodipine maleate corresponds to 1.0 to 25 mg of amlodipine free base.

13. The composition according to claim 12, wherein said amount of amlodipine maleate corresponds to 1.25, 2.5, 5 or 10 mg of amlodipine free base.

14. A method for treating or preventing angina, hypertension, or heart failure, which comprises administering to a patient in need thereof an effective amount of the composition according to claim 1.

15. A process for making the composition according to claim 1, which comprises mixing amlodipine maleate and at least one pharmaceutically acceptable excipient to form a mixture having a pH within the range of 5.5 to 6.8.

16. A process, which comprises:

mixing amlodipine maleate and at least one pharmaceutically acceptable excipient to form a mixture having a pH of 5.5-6.8.

17. The process according to claim 16, which further comprises compressing said mixture into a tablet.

18. The process according to claim 16, which further comprises filling capsules with said mixture to form a pharmaceutical dosage form.

19. The process according to claim 16, wherein said mixing is carried out by wet granulation.

20. The process according to claim 16, wherein said mixing is carried out by a dry method.

21. The process according to claim 20, wherein said amlodipine maleate is mixed as solid particles having an average particle size of at least 100 microns with said excipient.

22. A tablet made according to the process of claim 16.

23-27 (cancelled).

28. The composition according to claim 8, wherein said pH adjusting agent is a pharmaceutically acceptable acid.

29. The composition according to claim 28, wherein said pharmaceutically acceptable acid is maleic acid, citric acid, or ascorbic acid.

30. The composition according to claim 29, wherein said pharmaceutically acceptable acid is maleic acid.

31. The composition according to claim 1, wherein said composition comprises an acidic excipient.

32. The composition according to claim 1, wherein said amlodipine maleate has an average particle size of at least 20 microns.

33. The composition according to claim 32, wherein said amlodipine maleate has an average particle size of at least 100 microns.

34-36 (not entered).

37. The composition according to claim 1, wherein said composition has a pH within the range of about 5.5-6.2.

38. The composition according to claim 1, wherein said composition has a pH within the range of about 6.0-6.2.

39. The composition according to claim 9, wherein said composition has a pH within the range of about 5.5-6.2.

40. The composition according to claim 1, wherein said excipient is pH inert.

41. The composition according to claim 40, wherein said excipient is microcrystalline cellulose.

42. The composition according to claim 1, wherein at least one excipient is an acidic excipient.

43. The composition according to claim 42, wherein said acidic excipient is a sodium starch glycolate.

44. The composition according to claim 43, which further comprises microcrystalline cellulose.

45. The composition according to claim 44, wherein the sum of excipients other than said microcrystalline cellulose is less than 10 wt% based on the total weight of the composition.

46. The composition according to claim 43, which further comprises a calcium phosphate.

47. The composition according to claim 46, wherein the sum of excipients other than said calcium phosphate is less than 10 wt% based on the total weight of the composition.

EXHIBIT A

Excerpts from the Handbook of Pharmaceutical Excipients, 3rd Ed. relating to dibasic calcium phosphate. This information was filed with the Amendment of December 4, 2003 and was cited on page 11 thereof.

Handbook of PHARMACEUTICAL EXCIPIENTS

Third Edition

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Calcium Phosphate, Dibasic Anhydrous

1. Nonproprietary Names

BP: Calcium hydrogen phosphate
PhEur: Calcii hydrogenphosphas anhydricus
USP: Dibasic calcium phosphate
JP: Anhydrous dibasic calcium phosphate

2. Synonyms

A-TAB; calcium orthophosphate; calcium monohydrogen phosphate ; dicalcium orthophosphate; *Di-Cafos AN*; E341; E540; *Anhydrous Emcompress*; phosphoric acid calcium salt (1:1); secondary calcium phosphate.

3. Chemical Name and CAS Registry Number

Dibasic calcium phosphate [7757-93-9]

4. Empirical Formula and Molecular Weight

Empirical Formula	Molecular Weight
$CaHPO_4$	136.06

5. Structural Formula

$CaHPO_4$

6. Functional Category

Tablet and capsule diluent.

7. Applications in Pharmaceutical Formulation or Technology

Anhydrous dibasic calcium phosphate is used both as an excipient and as a source of calcium in nutritional supplements. It is used particularly in the nutritional/health food sectors. It is also used in pharmaceutical products because of its compaction properties, and the good-flow properties of the coarse-grade material. The predominant deformation mechanism of anhydrous dibasic calcium phosphate coarse-grade is brittle fracture and this reduces the strain-rate sensitivity of the material, thus allowing easier transition from the laboratory to production scale. However, unlike the dihydrate, anhydrous dibasic calcium phosphate when compacted at higher pressures can exhibit lamination and capping. This phenomenon can be observed when the material represents a substantial proportion of the formulation and is exacerbated by the use of deep concave tooling.[1] This phenomenon also appears to be independent of rate of compaction.

Anhydrous dibasic calcium phosphate is abrasive and a lubricant is required for tableting, for example 1% magnesium stearate or 1% sodium stearyl fumarate.

Two particle-size grades of anhydrous dibasic calcium phosphate are used in the pharmaceutical industry. Milled material is typically used in wet-granulated or roller-compacted formulations. The 'unmilled' or coarse-grade material is typically used in direct-compression formulations.

Anhydrous dibasic calcium phosphate is nonhygroscopic and stable at room temperature. It does not hydrate to form the dihydrate.[2]

Anhydrous dibasic calcium phosphate is used in toothpaste and dentifrice formulations for its abrasive properties.

8. Description

Anhydrous dibasic calcium phosphate is a white odorless, tasteless powder or crystalline solid. It occurs as triclinic crystals.

9. Pharmacopeial Specifications

Test	JP	PhEur	USP
Identification	+	+	+
Characters	+	—	—
Description and solubility	—	+	+
Loss on ignition	—	—	6.6-8.5%
Loss on drying	—	—	≤ 1.0%
Acid insoluble substance	≤ 0.05%	—	≤ 0.2%
Heavy metals	≤ 31 ppm	≤ 40 ppm	≤ 0.003%
Lead			≤ 5 ppm[a]
Chloride	≤ 0.248%	≤ 330 ppm	≤ 0.25%
Fluoride		≤ 100 ppm	≤ 0.005%
Sulfate	≤ 0.200%	≤ 0.5%	≤ 0.5%
Carbonate	Absent	Absent	Absent
Barium	Absent	Absent	Absent
Arsenic	≤ 2 ppm	≤ 10 ppm	≤ 3 ppm
Monocalcium and tricalcium phosphates	—	14.0-15.5 ml	—
Organic volatile impurities	—	—	+
Iron	—	≤ 400 ppm	—
Assay (dried basis)	—	98.0-101.0%	98.0-105.0%

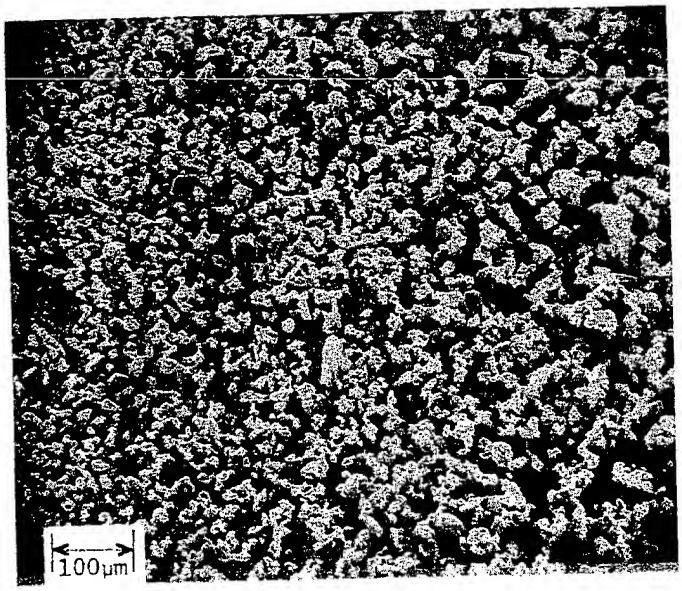
[a] California Proposition 65 agreement: from April 1999 the limit for lead (Pb) in dibasic calcium phosphate dihydrate used in multimineral and/or multivitamin supplements will be ≤ 0.4 ppm based on current US RDA for elemental calcium. The limit for anhydrous dibasic calcium phosphate has not yet been agreed.

10. Typical properties

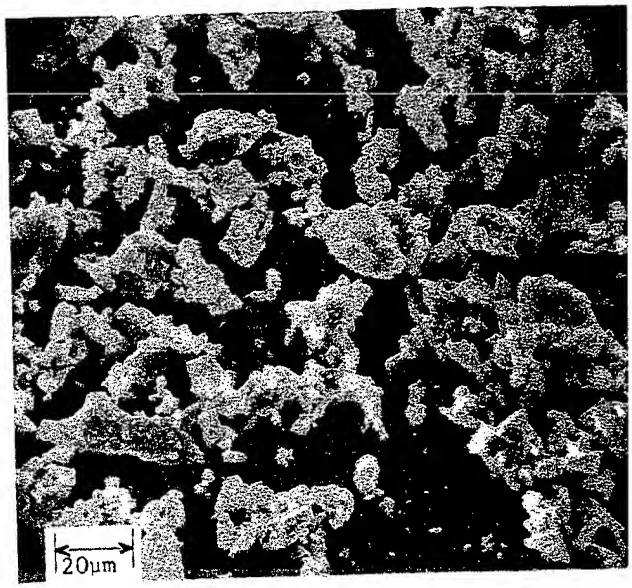
Acidity/alkalinity:
pH = 7.3 (20% slurry)
pH = 5.1 (20% slurry of *A-TAB*)
Compressibility: *See* Fig. 1.[a]
Density: 2.89 g/cm^3
Density (bulk): 0.78 g/cm^3 for *A-TAB*
Density (tapped): 0.82 g/cm^3 for *A-TAB*
Flowability: 18.9 g/s for *A-TAB*
Melting point: does not melt; decomposes at ≈ 425°C to form calcium pyrophosphate.
Moisture content: 0.1-0.187%,[a] the anhydrous material only contains surface adsorbed moisture. It cannot be rehydrated to form the dihydrate.
Particle size distribution:
Average particle diameter
180 µm for *A-TAB*;
136 µm for *Encompress Anhydrous*;
15 µm for powder.
Solubility: practically insoluble in ether, ethanol, and water; soluble, in dilute acids.
Specific surface area: 20-30 m^2/g for *A-TAB*

[a] *Handbook of Pharmaceutical Excipients*. First Edition.

SEM: 3
Excipient: Dibasic calcium phosphate dihydrate
Manufacturer: Stauffer Chemical Co
Lot: 16A-1 (89)
Magnification: 120×



SEM: 4
Excipient: Dibasic calcium phosphate dihydrate, coarse grade
Manufacturer: Stauffer Chemical Co
Lot: 16A-1 (89)
Magnification: 600×



9. Pharmacopeial Specifications

Test	JP	PhEur	USP
Identification	+	+	+
Characters	—	+	—
Description and solubility	+	—	+
Loss on ignition	—	—	24.5-26.5%
Loss on drying	19.5-22.0%	—	—
Acid insoluble substances	≤ 0.05%	—	≤ 0.2%
Heavy metals	≤ 31 ppm	≤ 40 ppm	≤ 0.003%
Chloride	≤ 0.248%	≤ 330 ppm	0.25%
Fluoride	—	≤ 100 ppm	≤ 50 ppm
Sulfate	≤ 0.160%	≤ 0.5%	≤ 0.5%
Carbonate	+	+	+
Barium	+	+	+
Arsenic	≤ 2 ppm	≤ 10 ppm	≤ 3 ppm
Monocalcium and tricalcium phosphates	—	+	—
Organic volatile impurities	—	—	+
Iron	—	≤ 400 ppm	—
Assay	—	98.0-101.0%	98.0-105.0%

10. Typical Properties

Acidity/alkalinity:
pH = 7.4 (20% slurry of *DI-TAB*)

Angle of repose: 28.3° for *Emcompress*.[6]

Compressibility: *See* Figs. 1, 2, 3, and 4.[a]

Compression pressure:	39.46 kN/cm^2
Tensile strength:	0.5605 kN/cm^2
Permanent deforation:	66.7 kN/cm^2
Brittle fracture:	0.1014
Reduced modulus of elasticity:	7917

Density (bulk): 0.915 g/cm^3[b]

Density (tapped): 1.17 g/cm^3[b]

Density (true): 2.389 g/cm^3[b]

Flowability:
27.3 g/s for *DI-TAB*;
11.4 g/s for *Emcompress*.[6]

Melting point: decomposes below 100°C with los
water.[1-3]

Moisture content: dibasic calcium phosphate dihydrate
tains two molecules of water of crystallization whicl
be lost at temperatures below 100°C. *See also* Fig.

Particle size distribution:
Average particle diameter = ≈ 180 µm for *DI-TAB*;
Average particle diameter = ≈ 9 µm for fine powder
See also Fig. 6.[a]

Solubility: practically insoluble in ethanol, ether, and
soluble in dilute acids.

Specific surface area: 0.44-0.46 m^2/g for *Encompress*.[b]

[a] *Handbook of Pharmaceutical Excipients*, First Edition.

[b] Results of laboratory project for third edition.

EXHIBIT B

FDA FOIA Material on Amlodipine Besylate, NDA No. 19-787, "Review of an Original NDA," October 1990. This information was filed in the Information Disclosure Statement of June 26, 2002. The 1449 form listing this document was initialed by the Examiner on October 29, 2002.

HFD-1 HOL

Amlodipine Besylate
Tablets 2.5, 5, 10 mg
NDA 19-787
Reviewer: Ameeta Parekh, Ph.D.
PC
12-S, 1-D, 5-O

[redacted]

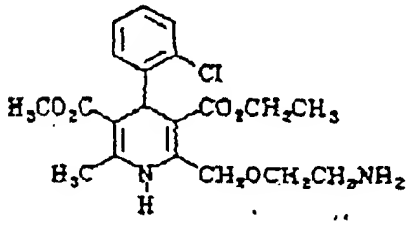
Pfizer Inc.,
Eastern Point Road
Groton, CT 06340
Submission Date:
December 22, 1987
August 2, 1988
February 22, 1990

OCT 10 1990

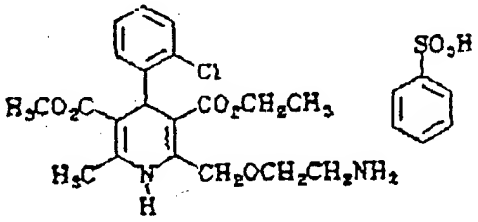
Review of an Original NDA

Background:

Amlodipine is a dihydropyridine antihypertensive and anti-anginal agent belonging to the class of calcium channel blockers. Amlodipine besylate is 3-ethyl-5-methyl-2-(2-amino ethoxymethyl)-4-(2-chlorophenyl) 1, 4-dihydro-6-methyl-3, 5-pyridinedicarboxylate benzenesulfonate, $C_{20}H_{25}ClN_2O_5C_6H_6O_3S$. The molecular weight of the base is 409 and the structure is



Amlodipine



Amlodipine besylate

Amlodipine besylate is a white crystalline substance slightly soluble in water (0.2% w/v at 24 °C) and sparingly soluble in ethanol.

The tablets to be marketed are formulated as white, round, normal convex, scored tablets containing 5 mg or 10 mg amlodipine for oral administration. All strengths (2.5, 5, 10mg) were made from a common direct compression blend.

The recommended dose is initially 5 mg once daily with a maximum of 10 mg. Steady state blood levels are reached after 7-8 days.

The amlodipine besylate tablets are intended to be manufactured at two sites, namely:

a) New York, USA
b) Barceloneta, Puerto Rico

In a telephone conversation with Dr.Hockel of Pfizer and Dr.Parekh of the Division of Biopharmaceutics, FDA, on June 8, 1988, the Sponsor informed that Pfizer originally intended to market the maleate salt of amlodipine. As a result, clinical studies were conducted with amlodipine maleate tablets and capsules (the capsules were used by the European counterparts). The maleate salt however, had formulation (tableting) and stability problems. The firm therefore switched to the besylate salt of amlodipine. In the submission dated 2/22/90, the firm stated that the maleate and besylate formulations used in the biopharm studies were also used in pivotal clinical studies. A list of formulations used in the clinical and bio studies is attached. It is not very clear as to what formulations were clinically tested. (The Medical Reviewer should be made aware of this stability problem of the maleate salt and its implications in safety and efficacy trials).

Studies Reviewed:

1. Open two-way cross-over study in normal male volunteers to study the pharmacokinetics of amlodipine maleate administered orally as capsules and by intravenous infusion. (Vol. 1.17, Study #208)

2. Open three-way cross-over study in healthy male volunteers, to study the pharmacokinetic properties of amlodipine maleate administered as solution and capsules and amlodipine benzene sulfonate administered as tablets. (Vol. 1.18, Study #214)

3. Open two-way cross-over study in healthy male volunteers to study the pharmacokinetic properties of amlodipine administered orally as the maleate salt in solution and as the benzene sulfonate salt in capsule formulations. (Vol. 1.18, Study #215)

4. Open two-way cross-over study in normal male volunteers to study the pharmacokinetics of amlodipine administered orally as the maleate salt in solution and in capsules. (Vol. 1.19, Study #203)

5. Double blind, placebo controlled, fourteen day evaluation of amlodipine 15 mg/day, administered to normal volunteers. (Vol. 1.19, Study # 209)

6. To study the pharmacokinetics of a range of oral doses of amlodipine in normal volunteers. (Vol. 1.17, Study #201)

7. An open dose-ranging evaluation of single intravenous doses of amlodipine administered to normal male volunteers. (Vol. 1.17, Study #205)

8. Pharmacokinetics of amlodipine in healthy volunteers: A three-way crossover comparison of 2.5, 5 and 10 mg single oral doses. (Vol. 1.22, Study #006)

9. Double blind, placebo controlled, sequential parallel group study of 7 days treatment at 3 dose levels of amlodipine capsules. (Vol. 1.21, Study #202)

10. An open study in normal male volunteers of the absorption, metabolism and excretion of radiolabeled amlodipine maleate given orally and intravenously. (Vol. 1.27, Study 206/207)

11. An open two-way crossover study in normal male volunteers to examine the effects of food on the pharmacokinetics of a single oral dose of amlodipine. (Vol. 1.23, Study #210)

12. An open study in elderly volunteers to examine the pharmacokinetics of a single dose of amlodipine administered orally by capsule. (Vol. 1.25, Study # 211/211A)

13. An open study to compare the pharmacokinetics of oral amlodipine in patients with renal insufficiency and in healthy subjects. (Vol.1.24-1.25, Study # 368)

14. To determine the pharmacokinetic profile of amlodipine after a single oral dose in patients with mild hypertension at dose levels ranging from 0.5 to 20mg. (Vol.1.16, Study # 001)

15. The pharmacokinetic interaction of amlodipine and digoxin in healthy volunteers. (Vol.1.23-1.24, Study # 005)

16. A two-way crossover study to evaluate the pharmacokinetics of a single oral dose of amlodipine when co-administered with single blind cimetidine or placebo to healthy volunteer subjects. (Vol.1.24, Study # 216)

17. Protein binding of (^{14}C]amlodipine in the plasma of rat, dog and man. (Vol.1.28)

18. Investigations on the protein binding of digoxin, indomethacin, phenytoin and warfarin to human plasma in the presence of amlodipine. (Vol.1.28)

19. In-vitro dissolution for amlodipine besylate tablets. (Vol.1.16)

20. Proportions of amlodipine enantiomers in human plasma. (Vol.1.28)

21. Review of the package insert. (Vol.1.1)

SUMMARY REPORT

General Pharmacokinetics in Humans: Amlodipine maleate administered as solution and capsule and amlodipine besylate administered as tablet and capsule were found to bioequivalent. Oral administration results in a slow absorption with a Tmax of about 6-13 hours, with a slow elimination half life of about 21-50 hours. The Tmax were similar between tablets, capsules and solutions. Intravenous administration of amlodipine results in a biphasic decline (Study 208, 205, 206/207) with a rapid distribution for about 4-6 hours, t1/2 of 0.1-0.26 hours, followed by slow elimination with a half-life of about 26-44 hours. The volume of distribution is high, about 1400 liters. The total plasma clearance was 646 ml/min. The pharmacokinetic parameters from different studies are summarized:

Study#	total oral dose, mg	N	Cmax ng/ml	AUC ng.hr/ml		t1/2 hours	Tmax hours	SD/MD
208	10 (mc)	12	5.86(1.18)	238(53)	0-inf	33.8	7.6(1.8)	SD
214	20 (mc)	17	11.55(3.1)	585(238)	0-inf	40.7(7.8)	9.4(2.9)	SD
	20 (bt)	17	11.64(3.3)	598(236)	0-inf	42.1(7.9)	9.2(1.9)	SD
	20 (ms)	17	11.62(3.5)	590(225)	0-inf	41.6	10(2.4)	SD
215	20 (bc)	12	8.76(2.74)	385(144)	0-192	43.6	7.3(1.6)	SD
	20 (ms)	12	8.36(2.42)	362(144)	0-192	43.9	7.3(1.8)	SD
203	20 (mc)	12	10.4(1.05)	464(100)	0-inf	37.8(7.1)	7.2(1)	SD
	20 (ms)	12	9.64(1.55)	456(116)	0-inf	37(7.6)	8.2(2)	SD
209	15(mc) day 1	28	6.93(2.6)		0-inf		8.9(3.7)	MD
	day 14	28	18.07(7.1)	348(139)	0-24	44.7(8.6)	8.7(1.9)	
201	10 (mc)	2	12.3, 7.6	390, 281	0-48		8, 8	SD
	15 (mc)	2	10.6, 9.4	245, 234	0-48	31, 21	6, 13	SD
	20 (mc)	2	10.5, 7.1	305, 157	0-48	29,	6, 13	SD
006	2.5 (bt)	12	1.26(0.26)	41(12.2)	0-72	31.2	5.4(1.7)	SD
	5.0 (bt)	12	2.66(0.54)	94.3(22)	0-72	33	6.3(3.1)	SD
	10 (bt)	12	5.49(1.31)	200(45)	0-72	36.8	6.4(2.7)	SD
	2.5 (bt)			54.3(19.7)	0-inf			
	5.0 (bt)			124(33.94)	0-inf			
	10 (bt)			279.5(82.6)	0-inf			
002	10(mc) day 1	6	4.7(1.1)	71(23)	0-24		7.7(2.7)	MD
	day 14	6	11(5.8)	217(119)	0-24	53.3	6(1.8)	
	15(mc) day 1	9	8(2.4)	121(36)	0-24		8(2.5)	MD
	day 14	9	6.9(2.5)	494(171)	0-24	53.3	6.9(2.5)	
202	2.5(mc) day 1	4	1.7(1.1)	21(9.3)	0-24		7.5(1)	MD
	day 7	4	3.3(1.3)	54.3(25)	0-24	27.5	8(2.8)	
	5.0(mc) day 1	4	3.6(1)	48.5(10.9)	0-24		8(2.8)	MD
	day 7	4	9.9(4.6)	169.6(94.8)	0-24	34.7	8.5(2.5)	
	7.5(mc) day 1	4	3.3(1)	50.2(20.3)	0-24		7(1.1)	MD
	day 7	4	11(5.9)	176(78)	0-24	35.5	8.5(2.5)	
206/207	15(C14)	2	6.7, 5.6	218, 261	0-inf	36, 30	8, 12	SD
210	10(mc) fast	12	4.26(1.24)	168(67)	0-144	41.3	8(2.4)	SD
	fed	12	4.38(1.16)	178(64)	0-144	39.8	8(1.9)	SD

m=maleate, b=besylate, c=capsule, t=tablet, s=solution, SD=single dose, MD=multiple dose, C14=radiolabel

Absorption, Distribution, Metabolism, Excretion: After single IV (2mg) and oral (15mg) doses of ^{14}C-amlodipine to 2 volunteers, absolute bioavailability of 60-65% was reported, indicating about 30% first pass. The total radioactivity in plasma was about 10 fold the unchanged drug and had nearly twice the terminal half-life. About 61% of the administered radioactivity was recovered in urine while fecal elimination accounted for about 20-25% of the radioactive dose. Similar % of the radioactive dose were recovered in the urine and feces after oral or IV administrations, indicating complete oral absorption. This, along with the patterns of plasma concentrations, indicate possibility of recirculation. Total recovery over 14 days in urine and feces was 76-90% of the dose. Nine (9) major metabolites were identified which, being the pyridine metabolites, are devoid of calcium antagonistic activity (it is recommended that this study be reviewed by the pharmacologist).

The plasma protein binding was studied at the concentrations 50 and 500 ng/ml, using equilibrium dialysis with pH 7.4 buffer at 37°C. Both concentrations are above the expected therapeutic concentrations. At these concentrations, amlodipine was found to be 97.5% and 96.2% resp. bound (in-vitro). In-vitro protein binding of digoxin, indomethacin, phenytoin and warfarin were studied in presence of amlodipine. A mean of 5 determinations showed that indomethacin, phenytoin and warfarin binding did not change in presence of amlodipine. Digoxin protein binding was 46(±3.3)% and in presence of amlodipine was 40.9(±3.4)%. If this change in the binding were significant, it did not influence the pharmacokinetics of either amlodipine or digoxin, as shown in the Study 005. (The assay validation for the RIA for digoxin was not submitted so the conclusion for digoxin is provisional).

Amlodipine is a racemic mixture of the R(-) (active isomer) and the S(+) isomers. The proportions of the enantiomers remained constant in the systemic circulation for upto 24 hours after a single oral dose of 20mg. The last sampling time was 48 hours, at which time the R:S ratio increased slightly (by about 7.5% and 11% in the 2 subjects studied). Since the drug half life is about 20-50 hours, this is only partial information on the relative pharmacokinetics of the individual isomers.

Dose Proportionality: Information from several studies was used in order to identify the dose proportionality (in the recommended dose range). Accumulation ratio of 2.6-3.6 (Study 209, 15mg/day for 14 days) is in accord with the theoretical prediction for linear drug with τ=24 hours and t1/2 of 45 hours. In Study 201, administration of 10, 15 and 20mg po to 2 subjects each, showed large variability between subjects. Although no dose related trend was seen, the study was inconclusive with regard to the dose proportionality due to the variability in the data. In Study 205, 1.25-15mg of amlodipine was administered IV in pairs. The plasma concentration profiles were biphasic with indications of recirculation. The pharmacokinetics were apparently linear based on the AUC(0-inf) for all subjects. In Study 006, 2.5mg, 5mg and 10mg were administered po as single doses crossed-over in 12 subjects. Dose proportionality could be concluded based on the 5mg and 10mg administrations, which are the recommended therapeutic doses. The dose normalized AUC from the 2.5mg dose were lower however, this may be attributed to low plasma concentrations in the region of the assay detection limit. Study # 202

was a parallel multiple dose, dose ranging study with 4 subjects in each dose group of 2.5, 5 and 7.5 mg q.d. for 7 days. The Cmax and AUC were proportionate to the dose. Study # 001 was in mildly hypertensive patients where 0.5-20mg were administered as incremental doses with 3-4 subjects at each dose. A linear increase in the AUC and Cmax with dose was observed, however, one of the three subjects studied at the 20mg dose showed a disproportionately high Cmax and AUC. The highest dose recommended however, is 10mg/day.

Food Effect on Pharmacokinetics: This was studied in 12 subjects and the "fed" state breakfast consisted of milk, bread and butter, bacon and decaffeinated coffee. Food did not effect the pharmacokinetics of amlodipine.

Special Populations: Pharmacokinetics of amlodipine were investigated in 'healthy' elderly males and females (Study 211/211A), in patients with different degrees of renal dysfunction (Study 368) and in patients with mild hypertension (Study 001).

Study#	Population	N	Dose,mg	Cmax	AUC	Tmax	t1/2
211/211A	elderly						
	male	8	5 (mc)	2.46(0.3)	161(55) 0-inf	7(1.9)	46.9
	female	8	5 (mc)	4.1(1.37)	240.5(105) "	8.3(2.7)	43.3
368	renal failure GFR (ml/min)						
	38-65	6	5(mc) day 1	3.6(1.2)	58(19) 0-24	6(1.3)	
			day 14	10.9(2.8)	210(42)0-24	5(1.1)	52.1
	20-29	5	5(mc) day 1	3.5(1.4)	61(23) 0-24	8.4(3.3)	
			day 14	11.4(4.7)	262(63)0-24	6.4(1.7)	46.2
	7-15	6	5(mc) day 1	2.4(0.6)	39(11) 0-24	5.7(2)	
			day 14	6.2(3.2)	127(67)0-24	5.3(1.6)	41.7
	0-2	4	5(mc) day 1	2.3(0.3)	35(7) 0-24	5(2.6)	
			day 14	7.8(2.5)	147(59)0-24	6(1.6)	50.6
	104-126 (normal)	6	5(mc) day 1	2.5(1)	44(16) 0-24	9.3(3.3)	
			day 14	6.3(1.7)	118(36)0-24	7(3)	37.7
001	mild hypertension						
		3	1(mc)	0.8(0.2)		10.7(2.3)	
		4	2.5(mc)	1.6(0.8)		7(1.2)	
		4	5(mc)	2.2(0.3)	85(10) 0-72	8.5(2.5)	
		4	10(mc)	5.1(1.4)	171(42)0-72	8.5(2.5)	38.5
		4	15(mc)	5.5(1.5)	256(90)0-72	8.5(3.0)	63
		3	20(mc)	13.4(5.9)	428(232)0-72	6.7(1.2)	49.5

Elderly females showed nearly twice the Cmax and AUC of the elderly and young healthy males. The pharmacokinetics study in renally impaired patients showed that subjects with GFR ranging from 20-65 ml/min had higher Cmax and AUC than the normals on day 14. Patients with GFR ranging from 0-15 showed no Cmax and AUC differences from those of the normals. Hypertension did not influence the pharmacokinetics of amlodipine.

Drug Interactions: Coadministration with either digoxin (Study 005) or cimetidine (Study 216) did not influence the pharmacokinetics of amlodipine.

Assay procedure: A gas chromatograph fitted with a capillary column and an electron capture detector were used for analyzing human plasma. The method involved injection of the trimethylacetyl derivative of amlodipine and the internal standard (UK-52,829). The accuracy and reproducibility were evaluated with each study. Generally, with each biopharmaceutics study, the plasma samples were analyzed in batches comprising of all samples from one subject with daily calibration standards, and approximately 10% of the total number of test samples as quality control standards. Approximately 10% repeat analyses were also performed.

Overall Comments:

1. Pfizer originally intended to market the maleate salt of amlodipine. I was informed that the the maleate salt had tableting and stability problems and the final marketed product was thus the besylate salt of amlodipine. Upon enquiring with the firm, I was informed (Supplement dated 2/22/90) that the maleate and besylate salts used for the biopharm studies were also used in pivotal clinical studies; this however is not very obvious from the submitted list of products used in these studies. The Chemist and the Medical Reviewer should be informed of this; its implications in terms of the clinical safety and efficacy studies should be evaluated by the Clinician; please refer to the ATTACHMENT at the end of the review.

2. Upon administration of C14-amlodipine, total radioactivity was 10 times higher than the radioactivity allocated to the parent drug. The half life for total radioactivity was also higher, about 100 hours. Nine major metabolites were identified. The firm has stated that these are the pyridine metabolites and therefore devoid of Ca-antagonistic activity. The pharmacologist is requested to review the Study # 206/207, Vol. 1.27 which supports this claim.

3. A study in normotensive elderly subjects conducted over two periods of time separated by about 1 year showed that the Cmax and AUC parameters for elderly females were about 2 times those of the elderly and young healthy males. This observation is made based on the study using 8 subjects each of elderly males and females and cross study comparison with young healthy male subjects. This information should be forwarded to the medical officer.

4. Patients with mild hypertension were studied at doses ranging from 0.5 to 20 mg single doses. The results represent combined data from 2 centers. About 3 or 4 patients were studied at each dose. The clinician should be informed that although dose proportionate AUC and Cmax were observed upto the 15mg dose, one of the three subjects studied at 20mg dose showed a disproportionately high AUC and Cmax. (Also note that the 20mg dose is higher than the daily recommended dose).

5. Although metabolism is a major pathway of elimination, hepatic patients have not been investigated.

6. The in-vitro protein binding was studied at 50 and 500ng/ml concentrations. These are higher than the therapeutic concentrations observed in the submitted studies. Protein binding should be studied at concentrations in the therapeutic range.

7. In-vitro dissolution should be characterized in various pH media. Based on the current dissolution data, the specification proposed is too liberal since almost 100% of the drug dissolved by 30 minutes. A specification of NLT 85% at 30 minutes would be more appropriate.

EXHIBIT C

Declaration under 37 C.F.R. § 1.132 of Ing Arlette Vanderheijden. This Declaration was filed on September 5, 2003 and was entered by the Examiner in the Advisory Action dated September 12, 2003.

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Jacobus M. LEMMENS *et al.*	:	Examiner: S. GOLLAMUDI
Serial No.:	09/938,816	:	Group: 1616
Filed:	August 27, 2001	:	
For:	PHARMACEUTICAL COMPOSITIONS COMPRISING AMLODIPINE MALEATE		

DECLARATION UNDER 37 C.F.R.§ 1.132

I, Ing. Arlette Vanderheijden, do hereby declare as follows:

1. I am a co-inventor in the above-identified U.S. patent application.
2. In 1995 I completed my Higher Laboratory Education (Hoger Laboratorium Onderwijs) studies at Hogeschool Heerlen[1], in Sittard, The Netherlands in Organic Chemistry. I earned the title, "Ing." which I believe is equivalent to a Bachelor of Science degree in the U.S.
3. In 1997 I became employed by Synthon BV, the assignee of the present application, and have remained so to the present. I am presently a project manager and part of my responsibilities includes studying amlodipine maleate pharmaceutical compositions.
4. I am aware that the Examiner has rejected all claims in the present application over Davison, U.S. Patent 4,879,303, in combination with several other patents. I further understand that the Examiner's position is that Davison teaches pharmaceutical compositions should have "a pH of close to that of blood (7.4)" in column 2 lines 28-29. It is my understanding that the Examiner requested a comparison with a composition having a pH of about 7.4.
5. Accordingly, the following experiments were carried out under my direct supervision and control.

   Six tablet blends (A-F) having the nominal composition as shown in Table 1 were compressed into tablets. The theoretical and the calculated/measured amounts for both the batch and tablet of each blend are set forth in Appendix 1.

[1] The School has since changed its name to Hogeschool Zuyd.

The tablet blends were made by the same methodology wherein the amlodipine maleate and all excipients except magnesium stearate were transferred to a free fall mixer and mixed for fifteen (15) minutes. Then the magnesium stearate was added and the blend was mixed for another three (3) minutes. A sample from each blend was removed and the pH in a 20 wt% aqueous slurry was determined.

Table 1

	Blend A (mg)	Blend B (mg)	Blend C (mg)	Blend D (mg)	Blend E (mg)	Blend F (mg)
pH	7.2	6.36	6.07	5.95	5.8	5.19
Amlodipine Maleate	6.42	6.42	6.42	6.42	6.42	6.42
Microcystalline Cellulose	124.18	124.48	124.56	124.58	124.43	123.855
CalciumhydrogenPhosphate Anhydrous	63.0	63.0	63.0	63.0	63.0	63.0
Sodium Starch Glycolate	4.0	4.0	4.0	4.0	4.0	4.0
Magnesium Stearate	2.0	2.0	2.0	2.0	2.0	2.0
Magnesium Oxide	0.4	0.1	0.02	-	-	-
Maleic Acid	-	-	-	-	0.15	0.725
Total	200	200	200	200	200	200

The blends were compressed into tablets of about 200 mg using 8 mm round punches in an EK0 excenter press. The compression force was about eight (8) kN. Samples of each tablet were stored for one month in a stability room under hot (60°C) or humid (40°C and 75% relative humidity) conditions in order to carry out an accelerated stability study. Additional samples were stored for one month at 4°C as a baseline. The tablets were placed in the stability room loaded in containers without closures, i.e. so-called "open dish." After storage for one month the tablets from the three storage conditions (two accelerated and one baseline) were analyzed by a validated HPLC method for various impurities. The difference in the averaged values for several impurities between the baseline storage and the accelerated storage are summarized in Tables 2A and 2B.

Table 2A

Difference in Impurities Between 40°C/75% RH and Baseline After 1 month, Open Dish

	A pH 7.2	B pH 6.36	C pH 6.07	D pH 5.95	E pH 5.8	F pH 5.19
Δ Aspartate[1]	5.11	1.55	0.30	0.07	0.06	0.05
Δ Amide[2]	0	0	0	0	0.04	0.13
Δ Pyridine[3]	0.09	0.05	0.03	0.05	0.10	0.13
Δ Total Impurities	5.68	1.73	0.4	0.19	0.25	0.42

1. amlodipine aspartate (Z#204)
2. amlodipine amide (Z#205)
2. amlo-pyridine (Z#202)

Table 2B

Difference in Impurities Between 60°C and Baseline After 1 month, Open Dish

	A pH 7.2	B pH 6.36	C pH 6.07	D pH 5.95	E pH 5.8	F pH 5.19
Δ Aspartate	0.13	0.13	0.13	0.11	0.07	0.04
Δ Amide	0.11	0.11	0.10	0.08	0.41	0.85
Δ Pyridine	0.21	0.24	0.23	0.22	0.31	0.40
Δ Total Impurities	0.52	0.56	0.55	0.47	0.92	1.56

6. The data shows that compositions having a pH greater than 7 (e.g. tablet A) or less than 5.5 (e.g. tablet F) are more susceptible to increases in impurity during storage. Under warm and humid conditions the formation of aspartate is most pronounced in tablet A having a pH of 7.2. The total impurities are also highest in tablet A in comparison to the other tablets stored under the same conditions. Under hot conditions, the formation of the amide and pyridine impurities is highest in tablet F which has a pH of 5.19. Thus, the most robust tablets are between pH 5.5 to 7.

7. That tablets in this pH range would exhibit more favorable stability is unexpected over the prior Davison disclosure. Indeed, following the Examiner's

understanding, the pH of 7.2 should have provided good stability because it was close to that of blood. However, under warm and humid conditions, such a tablet exhibits the worst stability. Moreover, because Davison does not recognize the aspartate impurity nor that its mechanism of formation involves a Michael addition, there is no basis in Davison to predict that a pH of less than 7 would improve stability against aspartate formation. Accordingly, the above data shows unexpectedly superior results for the invention of the present application.

8. I hereby declare that all statements made herein of my own knowledge are true and that all statements based on information and belief are believed to be true and further that these statements have been made with the knowledge that willful false statements and the like so made are punishable by fine, imprisonment, or both under section 1001 of Title 18 of the United States Code and that such false statements may jeopardize the validity of the application or any patent issuing thereon.

A Vanderheijden — 03.09.2003

Ing. Arlette Vanderheijden — Date

Encl. Appendix 1

APPENDIX 1

Blend A	Theoretical amount per 250 tablets	Theoretical amount per tablet	Actual amount dispensed per 250 tablets	Actual amount calculated per tablet
pH			**7.20**	
ADP.mal	1.605 g	6.42 mg	1.608 g	6.432 mg
Microcrystalline cellulose	31.045 g	124.18 mg	31.077 g	124.308 mg
Calciumhydrogenphosphate anhydrous	15.75 g	63.00 mg	15.770 g	63.08 mg
Sodium starch glycolate	1.00 g	4.00 mg	1.013 g	4.052 mg
Magnesium stearate	0.50 g	2.00 mg	0.499 g	1.996 mg
Magnesium oxide	0.100 g	0.40 mg	97.9 mg	0.3916 mg
Maleic acid	-	-	-	
Total	**50.00 g**	**200.00 mg**	**50.0649 g**	**200.2596 mg**

Blend B	Theoretical amount per 250 tablets	Theoretical amount per tablet	Actual amount dispensed per 250 tablets	Actual amount calculated per tablet
pH			**6.36**	
ADP.mal	1.605 g	6.42 mg	1.605 g	6.42 mg
Microcrystalline cellulose	31.12 g	124.48 mg	31.10 g	124.40 mg
Calciumhydrogenphosphate anhydrous	15.75 g	63.00 mg	15.75 g	63.00 mg
Sodium starch glycolate	1.00 g	4.00 mg	0.986 g	3.944 mg
Magnesium stearate	0.50 g	2.00 mg	0.516 g	2.064 mg
Magnesium oxide	0.025 g	0.10 mg	26.5 mg	0.106 mg
Maleic acid	-	-	-	-
Total	**50.00 mg**	**200.00 mg**	**49.9835 g**	**199.934 mg**

Blend C	Theoretical amount per 250 tablets	Theoretical amount per tablet	Actual amount dispensed per 250 tablets	Actual amount calculated per tablet
pH			**6.07**	
ADP.mal	1.605 g	6.42 mg	1.607 g	6.428 mg
Microcrystalline cellulose	31.14 g	124.56 mg	31.15 g	124.60 mg
Calciumhydrogenphosphate anhydrous	15.75 g	63.00 mg	15.77 g	63.08 mg
Sodium starch glycolate	1.00 g	4.00 mg	0.99 g	3.96 mg
Magnesium stearate	0.50 g	2.00 mg	0.51 g	2.04 mg
Magnesium oxide	5.00 mg	0.02 mg	6.10 mg	0.0244 mg
Maleic acid	-	-	-	-
Total	**50.00 g**	**200.00 mg**	**50.0331 g**	**200.1324 mg**

Blend D	Theoretical amount per 250 tablets	Theoretical amount per tablet	Actual amount dispensed per 250 tablets	Actual amount calculated per tablet
pH			**5.95**	
ADP.mal	1.605 g	6.42 mg	1.606 g	6.424 mg
Microcrystalline cellulose	31.145 g	124.58 mg	31.164 g	124.656 mg
Calciumhydrogenphosphate anhydrous	15.75 g	63.00 mg	15.751 g	63.004 mg
Sodium starch glycolate	1.00 g	4.00 mg	1.01 g	4.04 mg
Magnesium stearate	0.50 g	2.00 mg	0.50 g	2.00 mg
Magnesium oxide	-	-	-	-
Maleic acid	-	-	-	-
Total	**50.00 mg**	**200.00 mg**	**50.031 g**	**200.124 mg**

Blend E	Theoretical amount per 250 tablets	Theoretical amount per tablet	Actual amount dispensed per 250 tablets	Actual amount calculated per tablet
pH			**5.80**	
ADP.mal	1.605 g	6.42 mg	1.605 g	6.42 mg
Microcrystalline cellulose	31.1075 g	124.43 mg	31.137 g	124.548 mg
Calciumhydrogenphosphate anhydrous	15.75 g	63.00 mg	15.75 g	63.00 mg
Sodium starch glycolate	1.00 g	4.00 mg	1.00 g	4.00 mg
Magnesium stearate	0.50 g	2.00 mg	0.50 g	2.00 mg
Magnesium oxide	-	-	-	-
Maleic acid	0.0375 g	0.15 mg	37.3 mg	0.1492 mg
Total	**50.00 g**	**200.00 mg**	**50.0293 g**	**200.1172 mg**

Blend F	Theoretical amount per 250 tablets	Theoretical amount per tablet	Actual amount dispensed per 250 tablets	Actual amount calculated per tablet
pH			**5.19**	
ADP.mal	1.605 g	6.42 mg	1.612 g	6.448 mg
Microcrystalline cellulose	30.96375 g	123.855 mg	30.954 g	123.816 mg
Calciumhydrogenphosphate anhydrous	15.75 g	63.00 mg	15.75 g	63.00 mg
Sodium starch glycolate	1.00 g	4.00 mg	1.06 g	4.24 mg
Magnesium stearate	0.50 g	2.00 mg	0.50 g	2.00 mg
Magnesium oxide	-	-	-	-
Maleic acid	0.18125 g	0.725 mg	180.7 mg	0.7228 mg
Total	**50.00 g**	**200.00 mg**	**50.0567 mg**	**200.2268 mg**